

Mesenchymal stem cell transplantation reverses multiorgan dysfunction in systemic lupus erythematosus mice and humans.

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Public Summary:

Systemic lupus erythematosus (SLE) is a common and potentially fatal autoimmune disease characterized by antibodies associated multi-organ injuries including renal, cardiovascular, neural, musculoskeletal, and cutaneous systems. SLE may cause the destruction of many organ tissues and accumulation of auto-reactive lymphocytes and immune complexes. Although disease severity and organ involvement vary significantly among SLE patients, abnormalities of T and B lymphocytes are universal. Moreover, SLE manifests multifaceted immune modulation, including both deficiency and hyperactivity of the immune system. A deeper understanding of the underlying pathology is crucial to develop optimal therapies for the restoration of immune homeostasis without compromising the protective immune response to pathogens. In addition to conventional medical therapies such as cyclophosphamide and mycophenolate mofetil, several new strategies have been developed targeting specific activation pathways relevant to SLE pathogenesis. For instance, B-cell-depleting therapies using the monoclonal antibodies rituximab and epratuzumab have benefitted a specific subpopulation of lupus patients. Recently, hematopoietic stem cell transplantation (HSCT) has been reported to improve disease activity in treatment-refractory SLE patients and reverse organ dysfunction in several animal models. Despite improved supportive care, aggressive immunosuppressive medical therapies, and new therapeutic interventions, a subset of SLE patients continues to suffer significant morbidity and mortality from active disease, with visceral organ involvement. Therefore, it is urgent to develop more effective therapy for SLE disorder, especially for treatment-refractory patients. Bone marrow mesenchymal stem cells (BMMSCs) are multipotent stem cells capable of differentiating into a variety of cell types including osteoblasts, chondrocytes, adipocytes, and myoblasts. BMMSCs play a critical role in modulating immune cells including T and B lymphocytes, dendritic cells, and natural killer cells. Transplantation of ex vivo-expanded BMMSCs proved effective in treating acute graft-versus-host-disease (GVHD) by inhibiting T lymphocyte function and ameliorating blood stem cell engraftment. A recent convergence of clinical and basic research has highlighted the potential of using BMMSCs to treat immune diseases. In this study, we found that deficiency of BMMSC function in SLE mouse model leads to impairment of the osteoblastic niche, which may correlate in part, to difficulty of reconstructing immune homeostasis in treatment-refractory SLE patients. Allogeneic BMMSC transplantation (MSCT) conferred significant therapeutic effects on SLE mice and treatment-refractory patients by reconstructing the osteoblastic niche and restoring immune homeostasis.

Scientific Abstract:

Systemic lupus erythematosus (SLE) is a multisystem autoimmune disease that, despite the advances in immunosuppressive medical therapies, remains potentially fatal in some patients, especially in treatment-refractory patients. Here, we reported that impairment of bone marrow mesenchymal stem cells (BMMSCs) and their associated osteoblastic niche deficiency contribute in part to the pathogenesis of SLE-like disease in MRL/lpr mice. Interestingly, allogeneic BMMSC transplantation (MSCT) is capable of reconstructing the bone marrow osteoblastic niche and more effectively reverses multiorgan dysfunction when compared with medical immunosuppression with cyclophosphamide (CTX). At the cellular level, MSCT, not CTX treatment, was capable to induce osteoblastic niche reconstruction, possibly contributing to the recovery of regulatory T-cells and reestablishment of the immune homeostasis. On the basis of the promising clinical outcomes in SLE mice, we treated four CTX/glucocorticoid treatment-refractory SLE patients using allogeneic MSCT and showed a stable 12-18 months disease remission in all treated patients. The patients benefited an amelioration of disease activity, improvement in serologic markers and renal function. These early evidences suggest that allogeneic MSCT may be a feasible and safe salvage therapy in refractory SLE patients.

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